

5 The subject matter claimed is:

1. A method for the treatment of an interferon-responsive disorder in a warm-blooded animal, which method comprises:

administering to the animal at least one interferon formulated for short-term use;

adjusting the dosage with the short-term formulation to increase therapeutic response
while simultaneously decreasing adverse side effects;

subsequently selecting a dosage to be administered as a long-term formulation
showing a controlled rate of release over time;

thereafter administering the long-term formulation to release the interferon at a
controlled rate over time;

and subsequently optionally adjusting the level of interferon released with an additional
long-term formulation to further maximize therapeutic response while simultaneously
minimizing adverse side effects.

2. The method of claim 1, wherein the animal is a human.

3. The method of claim 2, wherein the interferon is selected from natural or recombinant
alpha, beta, consensus, gamma, leukocyte, omega, or tau interferon or versions
thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has
been attached by covalent or non-covalent bonding, or mixtures thereof.

4. The method of claim 3, wherein the interferon-responsive disease is selected from viral
hepatitis C, viral hepatitis B, condyloma accuminata, hairy cell leukemia, malignant
melanoma, follicular lymphoma, AID's related Kaposi's sarcoma, multiple sclerosis,
chronic granulomatous disease, pulmonary fibrosis, and tuberculosis.

5. The method of claim 3, wherein the interferon-responsive disease is selected from viral
hepatitis C, viral hepatitis B, condyloma accuminata, hairy cell leukemia, malignant
melanoma, follicular lymphoma, AID's related Kaposi's sarcoma and the interferon is
selected from natural or recombinant alpha, consensus, leukocyte, omega or tau
interferon or versions thereof to which polyethylene glycol or a polyethylene glycol –
fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures
thereof.



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- 5 6. The method of claim 3, wherein the interferon-responsive disease is selected from chronic granulomatous disease, pulmonary fibrosis, and tuberculosis and the interferon is natural or recombinant gamma interferon or a version thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding.
- 10 7. The method of claim 3, wherein the disease is multiple sclerosis and the interferon is selected from alpha, beta, consensus, leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.
- 15 8. The method of claim 3, wherein the same interferon is administered in the short-term formulation as is administered in the subsequent long-term formulation of interferon.
- 20 9. The method of claim 2, wherein a first interferon is administered as a short-term formulation and a different interferon is subsequently administered in the long-term formulation.
- 25 10. The method of claim 2, wherein the short-term formulation and the long-term formulation are the same.
- 30 11. The method of claim 2, wherein the short-term formulation and the long-term formulation are two different formulations.
- 35 12. The method of claim 2, wherein more than one interferon is administered for short-term use, each interferon being in the same formulation or in different short-term formulations.
- 40 13. The method of claim 2, wherein more than one interferon is administered for long-term use, each interferon being with the same or with different long-term formulation.
- 45 14. The method of claim 2, wherein the short-term formulation is administered first and the long-term formulation is subsequently administered either with or without an overlap of dosing with the short-term and long-term formulations.
- 50 15. The method of claim 2, wherein the controlled release dosage per time unit selected for the long-term formulation is about equivalent to the dosage release over the time unit for the short-term formulation.

- 5 16. The method of claim 2, wherein the controlled release dosage per time unit selected for the long-term formulation is different than that administered with the short-term formulation.
17. The method of claim 2, wherein the short-term delivery formulation is delivered by an injection, an infusion, an implantable system, a transdermal delivery system, an oral
10 formulation, non-oral parenteral formulation, or an inhalational device.
18. The method of claim 2, wherein the long-term delivery formulation is an implantable or injectable, non-bioerodible device; an implantable or injectable bioerodible system; a transdermal delivery system; or a chronic intravascular infusion system.
19. The method of claim 18, wherein the interferon is selected from naturally occurring
15 alpha, beta, consensus, gamma, leukocyte, omega, or tau interferon, or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.
20. The method of claim 19, wherein the interferon is omega interferon.
21. A method for individualizing doses of an interferon in the treatment of interferon-
20 responsive disorders in a warm-blooded animal, which method comprises
- administering at least one interferon, formulated for short-term use, in a plurality of the animals
- adjusting the dosage with the short-term formulation to increase therapeutic response while simultaneously decreasing adverse side effects;
- 25 determining the most commonly identified optimal dosage over time in a sufficiently large population of the animals to define such dosage as a unit dose;
- subsequently, defining a long-term formulation for delivering such dosage over time as more unit-dose or a fraction thereof, such that, in aggregate, the optimal dosage identified during dosing with the short-term formulation can be approximated with the
30 unit-dose or fractional unit-dose combination using the long-term formulation to deliver the interferon in a controlled dose over time;
- selecting a dosage to be administered to an individual animal with a long-term delivery;

5 thereafter administering the long-term dosage with a long-term delivery system;

and subsequently adjusting, if necessary, the dosage over time with the long-term
formulation to further maximize therapeutic response with simultaneously minimizing
adverse side effects.

22. The method of claim 21, wherein the animal is a human.

10 23. The method of claim 22, wherein the interferon is selected from natural or recombinant
alpha, beta, consensus, gamma, leukocyte, omega, or tau interferon, or versions
thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has
been attached by covalent or non-covalent bonding, or mixtures thereof.

15 24. The method of claim 22, wherein the interferon-responsive disease is selected from
viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell
leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's
lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell
carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal
cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's
20 sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, and
tuberculosis.

25 25. The method of claim 22, wherein the interferon-responsive disease is selected from
viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell
leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's
lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell
carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal
cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's
30 sarcoma, and the interferon is selected from natural or recombinant alpha, consensus,
leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or
a polyethylene glycol – fatty acid moiety has been attached by covalent or non-
covalent bonding, or mixtures thereof.

26. The method of claim 22, wherein the interferon-responsive disease is selected from
chronic granulomatous disease, pulmonary fibrosis, and tuberculosis and the interferon
is natural or recombinant gamma interferon or a version thereof to which polyethylene

5 glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding.

27. The method of claim 22, wherein the disease is multiple sclerosis and the interferon is selected from alpha, beta, consensus, leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has
10 been attached by covalent or non-covalent bonding, or mixtures thereof.

28. The method of claim 22, wherein the same interferon is administered in the short-term formulation and in the long-term formulation.

29. The method of claim 22, wherein a first interferon is administered as a short-term formulation and a different interferon is administered as the long-term formulation.

15 30. The method of claim 22, wherein the same formulation is administered as the short-term formulation and the subsequent long-term formulation.

31. The method of claim 22, wherein the short-term formulation differs from the subsequent long-term formulation.

20 32. The method of claim 22, wherein more than one interferon is administered for short-term use, each interferon being in the same or in different short-term formulations.

33. The method of claim 22, wherein more than one interferon is administered for long-term use, each interferon being with the same or with different long-term delivery systems.

25 34. The method of claim 22, wherein the short-term formulation is administered first and the long-term formulation is subsequently administered either with or without an overlap of dosing with the short-term and long-term formulations.

35. The method of claim 22, wherein the controlled release dosage per time unit selected for the long-term formulation is about equivalent to the dosage release over the time unit for the short-term formulation.

30 36. The method of claim 22, wherein the controlled release dosage per time unit selected for the long-term formulation is different than that administered with the short-term formulation.



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- 5 37. The method of claim 23, wherein the short-term delivery formulation is selected from an injection, an infusion, an implantable system, a transdermal delivery system, an oral formulation, non-oral parenteral administration, or an inhalational device.
38. The method of claim 37, wherein the interferon is selected from naturally occurring alpha, beta, consensus, gamma, leukocyte, omega, or tau interferon, or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.
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39. The method of claim 22, wherein the long-term delivery formulation is selected from an implantable, non-erodible device; an implantable or injectable erodible system; a gel or other dispersion; a transdermal delivery system; a chronic intravascular infusion system; an oral formulation; or an inhalational device; and the like.
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40. The method of claim 39, wherein the interferon is selected from naturally occurring alpha, beta, consensus, gamma, leukocyte, omega, or tau interferon, or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.
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41. A method of manufacturing a long-term delivery device for delivering a drug over time, which method comprises
- preparing a long-term delivery device designed for delivery of a drug at a relatively constant rate over time, the rate being determined to be a unit rate designed for a patient to receive a standard dosage rate to treat a disease state in the patient treatable over time by the drug, and
- 25
- preparing a long-term delivery device designed for delivery of the same drug at a relatively constant rate over time, which rate is a fraction of the standard dosage rate, wherein each device is suitable for presentation to a patient in need thereof alone or in combination with an identical device or the other device, depending on the dosage rate or fractional dosage rate determined to be appropriate for the patient.
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42. The method of claim 41, wherein the rate of delivery of the drug from the reduced rate device is about fifty percent of the rate of delivery from the standard rate device.
43. The method of claim 41, which method further comprises

5 preparing dosing instructions for adjusting the rate of administration of the drug by employing one or a combination of devices to achieve the desired release rate of the drug for a patient depending on the patient's needs over time.

44. The method of claim 41, wherein the drug is an interferon.

10 45. The method of claim 44, wherein the interferon is selected from natural or recombinant alpha, beta, consensus interferon, gamma, leukocyte, omega, or tau interferon, or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.

46. The method of claim 41, wherein the disease state is an interferon-responsive disease.

15 47. The method of claim 46, wherein the interferon-responsive disease is selected from viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's
20 sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, tuberculosis.

25 48. The method of claim 47, wherein the drug is an interferon selected from natural or recombinant alpha, consensus, leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.

49. The method of claim 48, wherein the disease is hepatitis C and the interferon is omega interferon.

50. The method of claim 48, wherein the disease is hepatitis C and the interferon is an alpha interferon.

30 51. The method of claim 48, wherein the disease is hepatitis C and the interferon is a consensus interferon.

52. The method of claim 48, wherein the disease is hepatitis C and the interferon is a natural or recombinant interferon.



5 53. The method of claim 46, wherein the interferon-responsive disease is selected from chronic granulomatous disease, pulmonary fibrosis, and tuberculosis and the interferon is natural or recombinant gamma interferon or a version thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding.

10 54. The method of claim 44, wherein the disease is multiple sclerosis and the interferon is selected from alpha, beta, consensus, leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.

15 55. A kit useful for delivery of a relatively constant amount of a drug thereof over time, wherein the amount of drug delivered to an individual patient within a population of patients can be adjusted to the patient's individual needs for treatment, the kit comprising

20 (a) at least one long-term delivery device designed for delivery of a drug at a relatively constant rate over time, the rate being determined to be a unit rate as a standard dosage to treat a disease state in a patient in the population over time, and

25 at least one long-term delivery device designed for delivery of the same drug at a relatively constant rate over time, which rate is a fraction of the standard dosage rate, wherein each device in the kit is suitable for presentation to a patient in need thereof alone or in combination with an identical device or the other device, depending on the dosage rate determined to be appropriate for the patient, or

30 (b) at least two long-term delivery devices designed for delivery of the same drug at the same or different yet relatively constant rates over time, for which each rate is a fraction of the standard dosage rate, wherein each device in the kit is suitable for presentation to a patient in need thereof along or in combination with an identical device or the other device, depending on the dosage rate determined to be appropriate for the patient.

56. The kit of claim 55, wherein the rate of delivery of the drug from the fractional rate device is about thirty-three percent of the rate of delivery from the standard rate device.

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5 57. The kit of claim 55, which kit further comprises

dosing instructions for adjusting the rate of administration of the drug by employing a combination of devices to achieve the desired release rate of the drug for a patient depending on the patient's needs over time.

58. The kit of claim 55, wherein the drug is an interferon.

10 59. The kit of claim 55, wherein the interferon is selected from the following: natural or recombinant alpha, beta, consensus interferon, gamma, leukocyte, omega, or tau interferon, or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.

15 60. The kit of claim 55, wherein the disease state is an interferon-responsive disease.

61. The kit of claim 60, wherein the interferon-responsive disease is selected from viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, tuberculosis.

25 62. The kit of claim 61, wherein the drug is an interferon selected from natural or recombinant alpha, consensus, leukocyte, omega or tau interferon or versions thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding, or mixtures thereof.

63. The kit of claim 61, wherein the disease is hepatitis C and the interferon is omega-interferon.

30 64. The kit of claim 60, wherein the interferon-responsive disease is selected from chronic granulomatous disease, pulmonary fibrosis, and tuberculosis and the interferon is natural or recombinant gamma interferon or a version thereof to which polyethylene glycol or a polyethylene glycol – fatty acid moiety has been attached by covalent or non-covalent bonding.